Research

Household Fuel Use and the Risk of Gastrointestinal Cancers: The Golestan Cohort Study

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BACKGROUND: Three billion people burn nonclean fuels for household purposes. Limited evidence suggests a link between household fuel use and gastrointestinal (GI) cancers.

OBJECTIVES: We investigated the relationship between indoor burning of biomass, kerosene, and natural gas with the subsequent risk of GI cancers.

METHODS: During the period 2004–2008, a total of 50,045 Iranian individuals 40–75 years of age were recruited to this prospective population-based cohort. Upon enrollment, validated data were collected on demographics, lifestyle, and exposures, including detailed data on lifetime household use of different fuels and stoves. The participants were followed through August 2018 with <1% loss.

RESULTS: During the follow-up, 962 participants developed GI cancers. In comparison with using predominantly gas in the recent 20-y period, using predominantly biomass was associated with higher risks of esophageal [hazard ratio (HR): 1.89; 95% confidence interval (CI): 1.02, 3.50], and gastric HR: 1.83; 95% CI: 1.01, 3.31) cancers, whereas using predominantly kerosene was associated with higher risk of esophageal cancer (HR: 1.84; 95% CI: 1.10, 3.10). Lifetime duration of biomass burning for both cooking and house heating (exclusive biomass usage) using heating-stoves without chimney was associated with higher risk of GI cancers combined (10-y HR: 1.14; 95% CI: 1.07, 1.21), esophageal (10-y HR: 1.19; 95% CI: 1.08, 1.30), gastric (10-y HR: 1.11; 95% CI: 1.00, 1.23), and colon (10-y HR: 1.26; 95% CI: 1.03, 1.54) cancers. The risks of GI cancers combined, esophageal cancer, and gastric cancer were lower when biomass was burned using chimney-equipped heating-stoves (strata difference p-values = 0.001, 0.003, and 0.094, respectively). Duration of exclusive kerosene burning using heating-stoves without chimney was associated with higher risk of GI cancers combined (10-y HR: 1.05; 95% CI: 1.00, 1.11), and esophageal cancer (10-y HR: 1.14; 95% CI: 1.04, 1.26).

DISCUSSION: Household burning of biomass or kerosene, especially without a chimney, was associated with higher risk of some digestive cancers. Using chimney-equipped stoves and replacing these fuels with natural gas may be useful interventions to reduce the burden of GI cancers worldwide. https://doi.org/10.1289/EHP5907

Introduction

An estimated 3 billion people still cook and heat their homes using open fires or leaky stoves fueled by kerosene, biomass, or coal (WHO 2018). Combustion of these fuels produces multiple carcinogenic compounds that can be absorbed through the respiratory and digestive tracts. (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2010; Lam et al. 2012). The International Agency for Research on Cancer (IARC) has recognized indoor emissions from coal combustion as carcinogenic to humans (Group 1), based on sufficient evidence from human and animal studies that documented the increased lung cancer risk resulting from indoor coal burning (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2010). However, despite the widespread use of biomass and kerosene fuels involving almost 40% of the human population, there is inadequate information on these exposures and their carcinogenicity (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2010; IARC 2013; WHO 2018).

Limited evidence from case–control studies has shown a link between household burning of biomass or kerosene fuels and an increased risk of cancers in different sites, including the gastrointestinal (GI) tract, highlighting the need for prospective studies to evaluate this hypothesis (Gerhardsson de Verdier et al. 1992; Josyula et al. 2015; Kayamba et al. 2017; Okello et al. 2019; Reid et al. 2012; Sapkota et al. 2013). Given that GI cancers account for more than one-fourth of cancer incidence and one-third of cancer-related mortality worldwide (Bray et al. 2018), and the fact that their burden is higher in areas where the exposure to household fuel combustion is highest (Torre et al. 2016), thorough assessment of these exposures and their effects on the risk of GI cancers is needed.

The Golestan Cohort Study (GCS) provides an opportunity to investigate this relationship due to its large sample size being located in a region with high rates of GI cancers, its enrollment of a mostly rural population that uses kerosene and biomass fuels for household purposes, and limited confounding effects from drinking alcohol and smoking due to low consumption rates. Based on 505,865 person-years of follow up, we investigated the relationship between household use of different fuels and the risk of developing GI cancers in the GCS participants.

Methods

Study Population and Design

The design of the GCS has been described previously (Pourshams et al. 2010). The GCS is a prospective population-based cohort study of individuals 40–75 years of age residing in the Golestan province in northeast Iran. After completing the pilot phase and validity studies, the enrollment phase started in January 2004. During a 4-y period (until June 2008), 50,045 individuals were recruited to the GCS from rural and urban areas of Gonbad, Maraveh-tappeh, Kalaleh, and Aq-qala districts (Figure S1). The urban participants were selected randomly by systemic clustering, using household numbers, and they were then contacted and invited by trained staff to participate in the study. In the rural areas, all eligible people living in the 326 villages of the study area were contacted and invited to participate. This process was done using the primary health-care networks that are present in each group of villages and usually staffed by two local health-care workers (Pourshams et al. 2010).

Individuals who had been diagnosed with upper GI cancers before enrollment, those who were unwilling or unable to participate, and temporary residents were excluded. All participants provided an informed consent before enrollment in the study. The GCS was approved by the institutional review boards of the Digestive Disease Research Institute of Tehran University of Medical Sciences, the International Agency for Research on Cancer, and the U.S. National Cancer Institute.

Questionnaires and Data Gathering

Two validated questionnaires were completed for each participant: a detailed general questionnaire (collecting data on demographics, socioeconomic status (SES), and lifestyle, including the details of lifetime fuel use and various other exposures) (Pourshams et al. 2005, 2010), and a Food Frequency Questionnaire (FFQ) (Malekshah et al. 2006). The general questionnaire contained questions about any regular consumption of opium, cigarettes, and alcohol, as well as the duration, frequency, and consumption amount of each agent. We calculated the cumulative use of opium in nokhod-years (nokhod is a local unit for opium that equals 0.2 grams) and cigarette smoking in pack-years (a pack includes 20 cigarettes), by calculating the number of units used per day multiplied by the number of consumption years. Then, for opium use we categorized the participants as either never users, or for the users, the tertiles of the cumulative nokhod-years of opium use. For cigarette smoking, we categorized the participants as either never smokers or, for the smokers, the tertiles of the cumulative pack-years of smoked cigarettes. Because of the few numbers of participants who consumed alcohol, for this exposure we categorized the participants based only on ever or never regular consumption of alcohol.

To evaluate SES, we used the quartiles of a composite wealth score that was created using multiple correspondence analysis on the following variables: property ownership; structure and size of the house; vehicle ownership; and having a television, refrigerator, freezer, vacuum or washing machine at home. The detailed method for creating this wealth score has been published previously (Islami et al. 2009).

Validity and Reliability of the Questionnaires

The details of validation studies have been published previously (Abnet et al. 2004; Malekshah et al. 2006; Pourshams et al. 2005). Briefly, in the pilot phase of the study, 1,057 individuals were interviewed, and two months later a repeat interview was performed on 131 participants. The kappa statistics for the agreement between the two interviews were above 0.7 for most variables, including tobacco, nass, opium, and alcohol consumption (Pourshams et al. 2005). The validity of the questionnaire data about opium use was assessed in 150 subjects by comparing their questionnaire responses with the presence of codeine or morphine in their urine; the questionnaire responses had a sensitivity of 0.93 and a specificity of 0.89 for identifying subjects with these urinary opium metabolites (Abnet et al. 2004). There was also a good agreement between self-reported current tobacco smoking or nass use and positive urinary cotinine (Pourshams et al. 2005). To validate the FFQ, 12 24-h recall questionnaires (one every month) and four FFQs (one in each season) were administered to 131 participants during 1 y. There was good correlation between FFQ and recall data on food group and nutrient intakes, and there was acceptable correlation between FFQ data and biomarker measurements (Malekshah et al. 2006). To examine the repeatability of the data collected in the actual cohort, we repeated the entire enrollment process, including interviews and sample collections, in 698 cohort participants from rural areas. The mean interval between the first and second enrollments was 45 months. The results showed very good agreement between data collected at the two interviews (Pourshams et al. 2005).

Assessment of the Main Exposure

Different types of fuels and stoves were used for household purposes in the Golestan region (Figure S2). In the study area, no cooking-stoves had chimney, although heating-stoves were available as chimney-equipped heating-stoves and heating-stoves without chimney. The participants (regardless of whether they cooked food themselves) were asked about the use of fuels in their household for cooking and for house heating throughout their lifetimes, using separate questions. The fuels were those available in the study area, including natural gas (liquefied petroleum gas), kerosene, and biomass (wood and animal dung). For each type of fuel, the participants were asked about their ages when the use of the specific fuel was started and, if applicable, was stopped in their households. The participants were also asked about the type of heating-stoves (chimney-equipped or without a chimney) that was used for house heating throughout their lifetimes.

Follow-up and Outcome Ascertainment

All participants have been followed since recruitment by active annual telephone surveys and home visits. Only <1% of the participants were lost to follow-up. In cases reporting incident cancers, a staff member visited the home of the patient to complete a questionnaire, and then a team was sent to the corresponding medical centers to gather copies of all relevant medical reports. All information was reviewed by two expert physicians to verify the diagnosis of cancer, and in case of disagreement, a third expert physician finalized the diagnosis. Cancer cases in the GCS were blindly matched to the Golestan Population-Based Cancer Registry database to avoid possible misclassifications of cancer cases. For this analysis, we included all GI cancers that were recorded in the follow-up through 1 August 2018. The final diagnosis of cancer and cause of death were recorded based on the 10th

revision of the *International Statistical Classification of Diseases and Related Health Problems (ICD-10)* (WHO 2016). All participants who developed GI cancers (ICD10 codes: C15–C26) during follow-up were included in this analysis. For gastric cancer, we further performed a subgroup analysis separating the cardia and noncardia subtypes. Because the majority of esophageal cancer cases were squamous cell carcinoma (>95%) we could not perform a subgroup analysis on adenocarcinoma subtype.

Statistical Analyses

We used Cox proportional hazards regression models to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for the association between household use of fuels and risk of GI cancers. Age was defined as the time scale, and the entry time was defined as the age at which the participant was recruited to the GCS. The exit time was defined as the age at which the participant was first diagnosed with any GI cancer for the GI cancer cases; the age at death for deaths from any other causes; and the age at the last follow-up for other participants, through 1 August 2018.

The covariates of the models were selected *a priori* based on the available literature to include the known risk factors for GI cancers in the study population and also the variables that might influence the assessed exposures (Shakeri et al. 2016; Sheikh et al. 2019). We used two models to analyze the data; the first model was used to analyze the lifelong durations of fuel usage and included age (10-y intervals/continuous), sex (male/female), ethnicity (Turkman/non-Turkman), residence (urban/rural), residence district (Gonbad/Maraveh-tappeh/Kalaleh/Aq-qala), quartiles of the composite wealth score, smoking cigarettes (never/tertiles of cumulative pack-years), opium consumption (never/tertiles of cumulative nokhod-years), and regular alcohol consumption (never/ever). The second model was used to analyze the recent usage of fuels and included all variables in the first model except residence (urban/rural), which showed significant multicollinearity with recent fuel use. Further adjustment for diet (using healthy eating index score) and job type (indoor/outdoor) did not change the results, and therefore these variables were not included in the main models.

Many participants had used different fuels through their lifetime, sometimes simultaneously (Tables S1 and S2). Therefore, to assess the relationship between household use of each fuel type and the risk of developing GI cancers, we used two different approaches. The first approach was used to compare the effects of recent usage of different fuels, with one fuel category as the reference group. For this purpose, based on the available literature we first defined *a priori* ranking of the different fuels, in terms of producing higher levels of carcinogenic compounds, as biomass > kerosene > gas (Adetona et al. 2013; Shen et al. 2017). Then, we defined a period of recent fuel usage as 20 y prior to enrollment and assigned each year during this period to the fuel that potentially produces highest levels of carcinogenic compounds. Finally, we calculated the proportion of time during the 20 y before enrollment for each fuel type, and assigned the participants to recent fuel use categories of "predominant biomass," "predominant kerosene," and "predominant gas" when >60% of the total 20 y was assigned to burning biomass, kerosene, and natural gas, respectively. The participants were categorized in the "none predominant (mixed fuels)" category if no single fuel reached >60% assignment in the total 20 y. Participants who had missing information on <8 y of the recent 20 y and had used a specific fuel for at least 12 y of the available duration were categorized into the predominant users of the corresponding fuel. We could not categorize the participants based on their recent usage of fuels if they had missing information on <8 y and did not report using any specific fuel for at least 12 y of the available duration, or if they had missing information on ≥8 y. Therefore, we removed these

participants (544 participants, including 8 GI cancer cases) from this analysis.

We used the other approach to assess the effects of long-term use of each fuel type throughout each participant's lifetime and also to assess whether the effects of each fuel type differed according to the type of heating-stoves (with/without chimney) that were used when burning the fuels for house heating. For this purpose, we first calculated the lifetime duration of using each fuel through cooking and through house heating separately, according to the reported starting and stopping ages. Then, we calculated the lifelong duration of using each fuel type regardless of its purpose (for cooking or for house heating). We observed strong correlations between the durations of using different fuels (Table S2), which was possibly due to the simultaneous usage of different fuels for house heating and for cooking in different time periods (Table S1). Thus, to have a better estimation of the effects of each fuel type, we calculated the durations of exclusive usage of each fuel that were not strongly correlated with each other (Table S3). The duration of exclusive usage of each fuel was defined as the period of using the corresponding fuel for both cooking and house heating. These variables were divided by 10 so that each unit corresponded to 10 y of exclusive usage of the fuels, and then those 10-y usage units were treated as continuous variables in the models to evaluate risk of cancer for each 10 y of exclusive household burning of the fuel. Because the participants had often used different fuels during their lifetimes, the durations of exclusive use of each fuel type were simultaneously included in the models that were used to assess the effects of long-term usage of fuels. We initially performed all analyses as overall use of different fuels, considering only the type of fuels and ignoring the type of heating-stoves. Then, we repeated all analyses considering the type of fuels used for cooking and house heating and also the type of heating-stoves (with/without chimney) used for house heating. Finally, we used the Wald test to assess whether the estimates from burning each specific fuel differ according to the type of used heating-stoves (with/without chimney).

For better interpretation of the results, we stratified the analyses of recent fuel usage by the reported SES on enrollment (having a wealth score below/above the median), and stratified the analysis of lifetime usage of fuels by sex (male/female), and used the interaction test to assess effect modifications. Sensitivity analyses were also performed by repeating the analyses after excluding the cases without histologic confirmation and also after dropping the first two years of follow-up to assess the possibility of reverse causality. All statistical analyses were performed using Stata statistical software version 14 (Stata Corp.).

Results

Baseline and Outcome Characteristics

A total of 50,045 participants were enrolled in the GCS; of these, 11 individuals (0.02%) had been diagnosed with GI cancers upon enrollment and were therefore excluded, leaving 50,034 participants for this analysis. During the follow-up, GI cancers were the most common cancers diagnosed in the GCS, accounting for 58.9% of the male cancer cases and 46.31% of the female cancer cases in this population. Of the 962 participants (1.92%) who were diagnosed with GI cancers, 782 (81.29%) had histologic confirmation, whereas 180 cases (18.71%) were identified through verbal autopsy and available medical records other than a histology report.

Participants who developed GI cancers tended to be older, have male gender, belong to the Turkman ethnicity, live in rural areas and the eastern districts, and have a lower wealth score (Table 1). Furthermore, in comparison with GI cancer incidence among the

Table 1. Baseline characteristics of all cohort participants and the individuals who developed gastrointestinal cancers during the follow-up period in the Golestan Cohort Study.

Baseline characteristics	GI cancer cases ($N = 962$) N (%) or mean $\pm$ SD	Cohort Participants ($N = 50,034$) N (%) or mean $\pm$ SD	p-Value
Age (y)	59.0 ± 9.1	52.0 ± 8.9	<0.001
Gender			<0.001
Male	579 (60.1)	21,228 (42.4)	
Female	383 (39.8)	28,806 (57.5)	
Ethnicity			<0.001
Turkman	777 (80.7)	37,245 (74.4)	
Non-Turkman	185 (19.2)	12,789 (25.5)	
Residence			<0.001
Rural	815 (84.7)	40,002 (79.9)	
Urban	147 (15.2)	10,032 (20.0)	
Residence districts			<0.001
Maraveh-tappeh	111 (11.5)	3,448 (6.8)	
Kalaleh	233 (24.2)	10,731 (21.4)	
Gonbad	555 (57.6)	30,298 (60.5)	
Aq-qala	63 (6.5)	5,557 (11.1)	
Wealth score[a]			<0.001
First quartile (lowest)	364 (37.8)	13,932 (27.8)	
Second quartile	218 (22.6)	11,144 (22.2)	
Third quartile	211 (21.9)	12,582 (25.1)	
Fourth quartile (highest)	169 (17.5)	12,376 (24.7)	
Smoking (pack-years)			<0.001
Never	723 (75.1)	41,378 (82.7)	
Lowest tertile (<5.7)	73 (7.5)	2,893 (5.7)	
Middle tertile (5.7–20)	70 (7.2)	2,993 (5.9)	
Highest tertile (>20)	96 (9.9)	2,770 (5.5)	
Opium consumption (nokhod-years)[b]			<0.001
Never	714 (74.2)	41,548 (83.0)	
Lowest tertile (≤9)	75 (7.8)	2,883 (5.7)	
Middle tertile (9.1–46)	72 (7.4)	2,784 (5.5)	
Highest tertile (≥46.5)	101 (10.5)	2,819 (5.6)	
Regular alcohol drinking			0.375
Never	924 (96.0)	48,325 (96.5)	
Ever	38 (3.9)	1,709 (3.4)	

Note: GI, gastrointestinal; N, number.
[a]Wealth score was previously created using multiple correspondence analysis on the ownership of house, vehicle, and some home appliances.
[b]Nokhod is a local unit for opium consumption that equals 0.2 grams of opium.

entire cohort, GI cancer incidence was higher among participants who smoked cigarettes and consumed opium (Table 1).

Characteristics of Household Fuel Use

Table 2 illustrates the distribution and characteristics of lifetime household fuel use in the study population. Almost all participants (99%) reported ever usage of gas for cooking and kerosene for heating in their lifetimes. Also, most participants reported

Table 2. Characteristics of the lifetime household fuel use for cooking and house heating purposes in the Golestan Cohort Study ($N = 50,034$).

Fuel and stove types	Purpose of use[a]	
	Cooking [N (%)]	House heating [N (%)]
Gas	49,591 (99.1)	17,458 (34.8)
Using stoves without chimney	49,591 (100.0)	77 (0.4)
Using chimney-equipped stoves	—	17,360 (99.4)
Using both stove types	—	21 (0.1)
Kerosene	18,064 (36.1)	49,562 (99.0)
Using stoves without chimney	18,064 (100.0)	6,905 (13.9)
Using chimney-equipped stoves	—	13,531 (27.3)
Using both stove types	—	29,126 (58.7)
Biomass	43,840 (87.6)	44,790 (89.5)
Using stoves without chimney	43,840 (100.0)	6,489 (14.4)
Using chimney-equipped stoves	—	31,918 (71.2)
Using both stove types	—	6,383 (14.2)

Note: —, no data; N, number.
[a]In the Golestan region, natural gas, kerosene, and biomass were burned for cooking and house heating purposes. In this area, no cooking-stoves had chimney, although heating-stoves were available as chimney-equipped heating-stoves and heating-stoves without chimney.

ever usage of biomass for cooking (87%) and for house heating (89%) (Table 2). Durations of burning gas for cooking and burning kerosene for house heating were positively correlated with each other, and negatively correlated with the durations of burning biomass for cooking and for house heating (Table S1).

In the study area, no cooking-stoves had chimney, whereas heating-stoves were available as chimney-equipped heating-stoves and heating-stoves without chimney. Almost all participants who reported ever usage of gas for house heating had reported burning gas using only chimney-equipped heating-stoves, whereas most participants who reported ever usage of kerosene for house heating had reported burning kerosene using both types of heating-stoves (with/without chimney), and most of those who reported ever use of biomass for house heating had reported burning biomass using only chimney-equipped heating-stoves (Table 2).

Household Fuel Use and Risk of GI Cancers Combined

We did not find strong associations between recent usage of household fuels and risk of GI cancers combined (Table 3). After stratifying the analysis by SES, a positive association between recent usage of biomass and risk of GI cancers combined was found among participants with higher SES (HR: 1.75; 95% CI: 1.04, 2.96) (Table S4).

Only lifetime duration of exclusive biomass burning was associated with increased risk of GI cancers combined (10-y HR: 1.10; 95% CI: 1.04, 1.16) (Table 4). After separating the durations of exclusive biomass burning according to the type of heating-stoves, burning kerosene using heating-stoves without chimney showed a

Table 3. Predominant fuel used for household purposes in the previous 20 y and risk of GI cancers ($N = 49{,}490$).

Predominant fuel type[a]	Case group [N (%)][b]	Non-case group [N (%)][b]	Adjusted[c] HR (95% CI)	p-Value
All GI cancers ($N = 954$)				
Gas	91 (9.5)	5,943 (12.2)	1	—
Nonpredominant	75 (7.8)	4,372 (9.0)	0.98 (0.72, 1.46)	0.923
Kerosene	685 (71.8)	34,786 (71.6)	1.15 (0.90, 1.73)	0.257
Biomass	103 (10.8)	3,435 (7.0)	1.25 (0.90, 1.34)	0.168
Esophageal cancer ($N = 341$)				
Gas	17 (4.9)	6,017 (12.2)	1	—
Nonpredominant	20 (5.8)	4,427 (9.0)	1.19 (0.62, 2.30)	0.591
Kerosene	261 (76.5)	35,210 (71.6)	1.84 (1.10, 3.10)	0.020
Biomass	43 (12.6)	3,495 (7.1)	1.89 (1.02, 3.50)	0.041
Gastric cancer ($N = 306$)				
Gas	23 (7.5)	6,011 (12.2)	1	—
Nonpredominant	24 (7.8)	4,423 (8.9)	1.25 (0.70, 2.24)	0.438
Kerosene	222 (72.5)	35,249 (71.6)	1.48 (0.93, 2.37)	0.097
Biomass	37 (12.0)	3,501 (7.1)	1.83 (1.01, 3.31)	0.043
Colon cancer ($N = 94$)				
Gas	22 (23.4)	6,012 (12.1)	1	—
Nonpredominant	8 (8.5)	4,439 (8.9)	0.53 (0.23, 1.22)	0.139
Kerosene	55 (58.5)	35,416 (71.7)	0.61 (0.33, 1.12)	0.117
Biomass	9 (9.5)	3,529 (7.1)	1.03 (0.40, 2.66)	0.936
Pancreatic cancer ($N = 78$)				
Gas	11 (14.1)	6,023 (12.1)	1	—
Nonpredominant	7 (8.9)	4,440 (8.9)	0.85 (0.32, 2.24)	0.754
Kerosene	54 (69.2)	35,417 (71.6)	0.83 (0.40, 1.73)	0.635
Biomass	6 (7.6)	3,532 (7.1)	0.75 (0.24, 2.32)	0.622
Liver cancer ($N = 69$)				
Gas	5 (7.2)	6,029 (12.2)	1	—
Nonpredominant	6 (8.7)	4,441 (8.9)	1.38 (0.41, 4.61)	0.601
Kerosene	52 (75.3)	35,419 (71.6)	1.36 (0.50, 3.69)	0.537
Biomass	6 (8.7)	3,532 (7.1)	1.16 (0.31, 4.37)	0.816

Note: —, no data; CI, confidence interval; HR, hazard ratio; N, number.
[a]Predominant fuel means that the fuel was used for ≥60% of the total time in the 20 y before enrollment.
[b]We could not identify recent fuel use for 544 (1.0%) participants of the cohort due to missing information, and therefore they were removed from this analysis.
[c]The model was adjusted for age (10-y intervals), sex, ethnicity (Turkman/non-Turkman), residence district (Gonbad/Maraveh-tappeh/Kalaleh/Aq-qala), wealth score quartiles, smoking cigarettes (never/tertiles of cumulative packyears), opium consumption (never/tertiles of cumulative nokhod-years), and regular alcohol consumption (never/ever).

positive association with the risk of GI cancers combined (10-y HR: 1.05; 95% CI: 1.00, 1.11). Furthermore, higher risk of GI cancers was observed among participants who burned biomass using heating-stoves without chimney than among those who burned biomass using chimney-equipped heating-stoves ($p < 0.001$) (Table 4). Stratifying the analysis by gender provided similar results among men and women (Table S5).

Household Fuel Use and Risk of Esophageal Cancer

Predominant usage of biomass (HR: 1.89; 95% CI: 1.02, 3.50), and kerosene (HR: 1.84; 95% CI: 1.10, 3.10) in the recent period were associated with higher risk of esophageal cancer, when compared with predominant usage of gas (Table 3). Stratifying the analysis by SES provided similar results among both strata (Table S4).

Lifetime durations of exclusive biomass (10-y HR: 1.12; 95% CI: 1.02, 1.23), and kerosene (10-y HR: 1.07; 95% CI: 0.99, 1.15) burning showed positive associations with increased risk of esophageal cancer (Table 4). After separating the durations of exclusive burning of fuels according to the type of heating-stoves, higher risk of esophageal cancer was observed among participants who burned biomass using heating-stoves without chimney than among those who burned biomass using chimney-equipped heating-stoves ($p = 0.003$) (Table 4). Further, higher risk of esophageal cancers was observed among participants who burned kerosene using heating-stoves without chimney but not in those who burned kerosene using chimney-equipped heating-stoves ($p = 0.032$) (Table 4). Stratifying the analysis by gender showed a positive association between the duration of exclusive kerosene burning and esophageal cancer only in women (Table S5), whereas positive associations

between the duration of exclusive biomass burning and esophageal cancer was observed in both men and women (Table S5).

Household Fuel Use and Risk of Gastric Cancer

Only predominant usage of biomass (HR: 1.83; 95% CI: 1.01, 3.31) in the recent period was associated with higher risk of gastric cancer, when compared with predominant usage of gas (Table 3). Stratifying the analysis by cardia and noncardia subtypes of gastric cancer (Table S6) and by SES (Table S4) did not provide meaningful differences between the strata.

Only lifetime duration of exclusive biomass burning was associated with increased risk of gastric cancer (10-y HR: 1.09; 95% CI: 1.00, 1.20) (Table 4). After separating the durations of exclusive burning of fuels according to the type of heating-stoves, slightly higher risk of gastric cancer was observed among participants who burned biomass using heating-stoves without chimney than among those who burned biomass using chimney-equipped heating-stoves ($p = 0.094$) (Table 4). Similar estimates were observed when we stratified the analysis by gender (Table S4). Stratifying the analysis by cardia and noncardia subtypes of gastric cancer showed a positive association between the duration of exclusive biomass burning using heating-stoves without chimney with both gastric cancer subtypes, whereas the duration of exclusive biomass burning using chimney-equipped heating-stoves was positively associated only with the cardia subtype (Table S7).

Household Fuel Use and Risk of Colon Cancer

Most participants who developed colon cancer had reported burning gas and kerosene as the predominant household fuels in the recent period. We did not find associations between recent usage

Table 4. Durations of exclusive use of fuels and risk of GI cancers in the Golestan Cohort Study ($N = 50,034$).

| | Overall | Using chimney-equipped heat stoves[b] | | |
| | | Yes | No | |
Fuel type[a]	Adjusted 10-y[d] HR (95% CI)	Adjusted 10-y[e] HR (95% CI)	Adjusted 10-y[e] HR (95% CI)	p-Value for the difference[c]
All GI cancers ($N = 962$)				
Gas	1.03 (0.83, 1.27)	1.05 (0.85, 1.29)	—	—
Kerosene	1.02 (0.96, 1.07)	0.96 (0.88, 1.04)	1.05 (1.00, 1.11)	0.218
Biomass	1.10 (1.04, 1.16)	1.04 (0.98, 1.11)	1.14 (1.07, 1.21)	0.001
Esophageal cancer ($N = 342$)				
Gas	0.86 (0.55, 1.35)	0.90 (0.57, 1.41)	—	—
Kerosene	1.07 (0.99, 1.15)	0.92 (0.80, 1.06)	1.14 (1.04, 1.26)	0.032
Biomass	1.12 (1.02, 1.23)	1.05 (0.96, 1.15)	1.19 (1.08, 1.30)	0.003
Gastric cancer ($N = 309$)				
Gas	0.88 (0.57, 1.34)	0.88 (0.58, 1.35)	—	—
Kerosene	0.99 (0.89, 1.09)	0.98 (0.84, 1.14)	0.97 (0.86, 1.09)	0.933
Biomass	1.09 (1.00, 1.20)	1.03 (0.93, 1.13)	1.11 (1.00, 1.23)	0.094
Colon cancer ($N = 95$)				
Gas	1.26 (0.78, 2.05)	1.29 (0.80, 2.10)	—	—
Kerosene	0.85 (0.68, 1.07)	1.01 (0.74, 1.39)	0.82 (0.61, 1.10)	0.425
Biomass	1.11 (0.91, 1.35)	1.12 (0.92, 1.37)	1.26 (1.03, 1.54)	0.226
Pancreatic cancer ($N = 78$)				
Gas	1.18 (0.65, 2.15)	1.18 (0.65, 2.14)	—	—
Kerosene	0.98 (0.80, 1.20)	1.12 (0.85, 1.47)	0.94 (0.74, 1.20)	0.451
Biomass	1.09 (0.89, 1.33)	1.12 (0.92, 1.37)	1.05 (0.84, 1.31)	0.501
Liver cancer ($N = 70$)				
Gas	1.16 (0.56, 2.38)	1.15 (0.56, 2.37)	—	—
Kerosene	0.91 (0.72, 1.15)	0.85 (0.58, 1.24)	0.95 (0.73, 1.23)	0.678
Biomass	1.11 (0.90, 1.37)	1.07 (0.86, 1.32)	1.07 (0.85, 1.35)	0.935

Note: —, no data; CI, confidence interval; HR, hazard ratio; N, number.

[a]Duration of exclusive use of fuels was defined as the duration of using the same fuel for both cooking and house heating.

[b]In the study area no cooking-stoves had chimney, whereas heating-stoves were available as chimney-equipped heating-stoves and heating-stoves without chimney.

[c]p-Value of the Wald test that compares the two estimates of the durations of exclusive use of fuels that are separated according to the type of the used heating-stoves (with/without chimney).

[d]This illustrates the HRs associated with every 10 y of using the indicated fuel, compared with those who never used that fuel. This model included age (10-y intervals), sex, ethnicity (Turkman/non-Turkman), residence (urban/rural), residence district (Gonbad/Maraveh-tappeh/Kalaleh/Aq-qala), wealth score quartiles, smoking cigarettes (never/tertiles of cumulative pack-years), opium consumption (never/tertiles of cumulative nokhod-years), regular alcohol consumption (never/ever), duration of exclusive gas burning (continuous), duration of exclusive kerosene burning, and duration of exclusive biomass burning (continuous).

[e]This illustrates the HRs associated with every 10 y of using the indicated fuel, compared with those who never used that fuel. This model included age (10-y intervals), sex, ethnicity (Turkman/non-Turkman), residence (urban/rural), residence district (Gonbad/Maraveh-tappeh/Kalaleh/Aq-qala), wealth score quartiles, smoking cigarettes (never/tertiles of cumulative pack-years), opium consumption (never/tertiles of cumulative nokhod-years), regular alcohol consumption (never/ever), duration of exclusive gas burning using chimney-equipped heating-stoves (continuous), duration of exclusive kerosene burning using chimney-equipped heating-stoves (continuous), duration of exclusive kerosene burning using heating-stoves without chimney (continuous), duration of exclusive biomass burning using heating-stoves without chimney (continuous), and duration of exclusive biomass burning using heating-stoves without chimney (continuous).

of household fuels and risk of colon cancer (Table 3). Stratifying the analysis by SES did not provide meaningful differences between the strata (Table S4).

Lifetime durations of exclusive fuel burning did not show significant associations with colon cancer (Table 4). After separating the durations of exclusive burning of fuels according to the type of heating-stoves, colon cancer showed a positive association with the duration of exclusive biomass burning using heating-stoves without chimney (10-y HR: 1.26; 95% CI: 1.03, 1.54), and a nonsignificant positive association with the duration of exclusive biomass burning using chimney-equipped heating-stoves (10-y HR: 1.12; 95% CI: 0.92, 1.37) (Table 4). Stratifying the analysis by gender showed a positive association between colon cancer and the durations of exclusive gas burning and exclusive biomass burning only in women (Table S5).

Household Fuel Use and Risk of Pancreatic and Liver Cancers

Most participants who developed pancreatic cancer and hepatobiliary cancers had reported burning kerosene, and very few reported burning gas and biomass as the predominant household fuels in the recent period. We did not find meaningful associations between recent usage of household fuels and risk of pancreatic and liver cancers (Table 3). Similarly, lifetime durations of exclusive burning of fuels did not show meaningful associations

with pancreatic and liver cancers (Table 4). Due to the limited number of participants who developed pancreatic and liver cancers, we could not include these cancer types in the stratified and sensitivity analyses.

Sensitivity Analyses

Repeating the analyses after dropping the first 2 y of follow-up (Tables S8 and S9) and after excluding cancer cases without histologic confirmations (Tables S10 and S11) provided very similar results.

Discussion

Analyzing the data on lifetime usage of household fuels from 50,000 participants of the GCS with more than 10 y of follow-up showed positive associations between household burning of biomass and kerosene fuels and increased cancer risk at some sites in the GI tract. Our study also found that using chimney-equipped heating-stoves while burning biomass or kerosene fuels were associated with lower risk of some GI cancers in comparison with burning the same fuels using heating-stoves without a chimney.

A working group from IARC evaluated the carcinogenic risks of biomass fuels to humans and concluded that household combustion of biomass fuels is probably carcinogenic to humans; however, the available evidence from human studies are limited and are

mainly derived from case–control studies (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2010; IARC 2013). An estimated 40% of the human population still burns biomass for cooking and/or house heating purposes (IARC 2013), so any evidence of cancer risk or adverse health effects associated with this exposure is concerning. Previously, we documented the increased risks of all-cause and cardiovascular disease mortalities (Mitter et al. 2016), as well as an increased risk of developing esophageal cancer associated with using nongas fuels (Sheikh et al. 2019). The current analysis further reveals that the potential effects of using nongas fuels may also extend to other parts of the GI system. In the current study, higher risks of esophageal and gastric cancers were observed in participants who burned biomass as the predominant household fuel in the recent 20 y when compared with participants who burned gas. Further, the duration of biomass usage for both cooking and house heating was positively associated with risks of GI cancers combined, esophageal cancer, gastric cancer, and colon cancer. An association between burning biomass fuels and esophageal cancer has previously been shown in case–control studies in Asia (Okello et al. 2019), Africa (Mlombe et al. 2015; Okello et al. 2019; Patel et al. 2013), Europe (Sapkota et al. 2013), and South America (Mota et al. 2013), and an association between indoor burning of biomass fuels and gastric cancer has been reported in two other case–control studies in Peru (Chirinos et al. 2012) and Honduras (Rifkin et al. 2015). We could not find studies assessing the association between the household use of biomass fuels and colon cancer; there is only some evidence of this association from occupational exposures, including studies that showed an increased risk of colon cancer in chimney sweepers and firefighters (Hogstedt et al. 2013; Youakim 2006), and an increased risk of rectal cancer in those with occupational exposure to the combustion of biomass fuels (Gerhardsson de Verdier et al. 1992).

Burning biomass fuels produces many harmful pollutants, some of which are recognized as carcinogens, including polycyclic aromatic hydrocarbons (PAH), benzene, and formaldehyde (IARC 2013), and these compounds can be absorbed through the skin, respiratory system, and GI tract (IARC 2013). Higher exposure to combustion of biomass fuels may increase the systemic absorption of these carcinogenic compounds, as documented in studies that have demonstrated high urinary levels of PAH metabolites, benzene, and carbon monoxide (CO) in individuals who were using biomass fuels (Fan et al. 2014; Long et al. 2014; Riojas-Rodriguez et al. 2011; Viau et al. 2000). In one study, an intervention with improved chimney-equipped stoves resulted in reduced urinary levels of PAH metabolites (Riojas-Rodriguez et al. 2011). In another study, DNA adducts, which indicate the presence of an effective dose of genotoxic compounds, mainly PAH (Agudo et al. 2012), were higher in women exposed to wood emissions than in those exposed to natural gas (Mumford et al. 1993). Further, there is some evidence that suggests a possible role for PAH in the pathogenesis of GI cancers (Diggs et al. 2011; Roshandel et al. 2012), including studies that showed high levels of PAH biomarkers in the urine or esophageal tissues of patients with esophageal cancer (Abedi-Ardekani et al. 2010; Roshandel et al. 2012) and in rectal tissues of patients with rectal cancer (Jiang et al. 2012). Studies that have shown higher levels of PAH-DNA adducts in patients with gastric, colorectal, and esophageal cancers (Agudo et al. 2012; Diggs et al. 2011; van Gijssel et al. 2004) further support this hypothesis. Therefore, it is plausible that intensive exposure to burning biomass fuels might cause GI cancers in different sites (Diggs et al. 2011).

Kerosene is another widely used fuel (Lam et al. 2012). An IARC working group evaluated the carcinogenic risks of kerosene in 1989 and concluded that there is limited evidence for its carcinogenicity (IARC Working Group on the Evaluation of Carcinogenic

Risks to Humans 1989). In comparison with burning biomass, burning kerosene may produce lower levels of PAH, CO, and fine particulate matter (PM). However, these compounds have been shown to be higher in the emissions from burning kerosene than from burning natural gas (Shen et al. 2017). Also, higher levels of PAH metabolites were found in the urine of individuals who were using kerosene fuels in comparison with those who were using natural gas (Adetona et al. 2013). In our study, indoor burning of kerosene was associated with significantly increased risk of esophageal cancer. We could not find other studies assessing GI cancer risks in individuals who burn kerosene for household use. A review of kerosene health hazards by Lam et al. indicated the paucity of studies on the relationship between this widespread exposure and cancer (Lam et al. 2012); the very few available case–control studies showed a relationship between kerosene use and increased cancer risk in the lung and salivary gland (Lam et al. 2012). There is also one occupational study that linked burning kerosene to increased rates of death from several digestive-tract cancers, including esophageal cancer (Ritz 1999).

Our study showed that using chimney-equipped heating-stoves when burning fuels is associated with lower risk of developing GI cancers, when compared with burning the same fuels using heating-stoves without chimney. The beneficial effects of proper house ventilation or using chimney-equipped stoves for burning fuels have also been shown for other cancers, including lung cancer (Jin et al. 2014; Kim et al. 2015; Lan et al. 2002). Li et al. analyzed urinary PAH metabolites in a subset of individuals who participated in a randomized trial of a home-based environmental intervention in Peru, and found significantly lower levels of urinary 2-naphthol (a suggested biomarker for inhalation PAH exposure) in the group that used chimney-equipped stoves in comparison with the group that used open fire stoves (Li et al. 2016). This finding was in line with other studies in Mexico, Peru, and Guatemala that evaluated different outcomes after replacing indoor stoves without chimneys with new chimney-equipped stoves and showed significantly reduced levels of PM and CO in personal air samples, decreased urinary PAH metabolites, decreased DNA damage, and decreased CO in the exhaled breath of the participants after the intervention (Díaz et al. 2007; Li et al. 2011; Torres-Dosal et al. 2008). These results show that when replacing the nonclean fuels with the clean ones is not feasible, replacing the traditional stoves without a chimney with the newer chimney-equipped stoves might be considered as an appropriate policy for lowering the health hazards associated with using nonclean fuels.

The strengths of this study are its prospective population-based design, large sample size, successful follow-up for more than 10 y of >99% of the participants, validated questionnaire data, validated cancer outcome data, detailed information on the lifetime history of household fuel use, and detailed information on the type of stoves used for burning the fuels. There are also some limitations in this study; similar to any observational study, we cannot rule out the potential errors in exposure and outcome measurements. However, due to the prospective design of this study, any error in measuring the exposure is likely to be nondifferential. Also, we tried to minimize the potential outcome measurements errors by matching the outcome data to the Golestan Population-based Cancer Registry data. Another limitation of the current study is the lack of quantifiable measures of household air pollution, including the level of organic carcinogenic compounds resulting from fuel combustions in the indoor air or the level of their metabolites in the urine. Further, despite the adjustments for potential confounders and performing different sensitivity and stratified analyses, we cannot exclude the possibility of residual confounding, especially for some cancer types (e.g., colon cancer) that showed inconsistent results and a modest risk increase in association with household

use of fuels. Also, the small number of cases in some cancer types (including colon, pancreatic, and liver cancers) and in some analytic strata may have resulted in spurious associations or unstable results, and therefore these results need to be interpreted with caution and should be investigated in further studies.

In conclusion, household burning of biomass and kerosene, especially without a chimney, may increase risk of some digestive-system cancers. Using chimney-equipped stoves and replacing these fuels with natural gas might be considered useful interventions to lower the risk of these cancers, especially in developing countries.

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